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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/863,600	05/23/2001	Virginia Smith-Swintosky	PRI-0014 (ORT-1436)	9298

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EXAMINER	
MOHAMED, ABDEL A	
ART UNIT	**PAPER NUMBER**
1653	

DATE MAILED: 11/20/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/863,600	SMITH-SWINTOSKY ET AL.	
	Examiner	Art Unit	
	Abdel A. Mohamed	1653	

-- The MAILING DATE of this communication appears on the cov r sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 August 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a)☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)

ce of Draftsperson's Patent Drawing Review (PTO-948)

mation Disclosure Statement(s) (PTO-1449) Paper No(s) *4*.

4)☐ Interview Summary (PTO-413) Paper No(s). _____.

5)☐ Notice of Informal Patent Application (PTO-152)

6)☐ Other: .

DETAILED ACTION

ACKNOWLEDGMENT FOR IDS, SEQUENCE LISTING, AMENDMENT, RESPONSE TO RESTRICTION REQUIREMENT AND STATUS OF THE CLAIMS

1. The Information Disclosure Statements (IDS) and Form PTO-1449 filed 12/1/01, the sequence listing filed 2/4/03 and the amendment and response to the restriction requirement filed 8/6/03, respectively are acknowledged, entered and considered. In view of Applicant's request, claims 9, 10 and 22 have been amended and claims 23-37 have been canceled. Thus, claims 1-22 are now pending in the application. Applicant's request to reconsider SEQ ID NOS:8, 19, 20, 17 and 21 to be examined in this application have been persuasive. Thus, the Office action is directed to the merits of elected Group I (claims 1-22) along SEQ ID NOS:8, 19, 20, 17 and 21 with their fragments thereof as *per* elected invention.

OBJECTION TO TRADEMARKS AND THEIR USE

2. The use of the trademarks "EPREX®", "ERYPO®", "PROCRIT®" and "NEORECORMON®" have been noted in this application. Although, the use of trademarks are permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in a manner, which might adversely affect their validity as trademarks. Further, the specification, which specifies the generic terminology should include, published product information sufficient to show that the generic terminology or the generic description are inherent in the article referred by the trademarks. These description requirements are made

because the nature and composition of articles denoted by trademarks can change and affect the adequacy of the disclosure.

CLAIMS REJECTION-35 U.S.C. 112 [1st] PARAGRAPH.

3. Claims 1-22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for employing peptides comprising one or more monomeric peptides that bind to erythropoietin (EPO) receptor and use of said peptides in designing, synthesizing and testing of biological activity toward the EPO receptor *in vitro*, does not reasonably provide methods of treating diseases or conditions of the nervous system in patients (which include humans) by administration of compositions having neurological therapeutic activity of EPO in the manner claimed in claims 1-22. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification does not adequately teach a method for treating a patient having a condition mediated by neurotoxicity, neurodegenaration or neurological damage, comprising administering to said patient a therapeutically effective amount of a peptide comprising one or more monomeric peptides of 8 to about 40 amino acids in length that bind to EPO receptor as presently claimed in claims 1-22; rather, the specification teaches the expression of rhEPO in primary rat neuronal cultures and in neuronal cell lines (Example 1), EPO induced gene expression in PC12 cells (Example 2), rhEPO neuroprotection and neurite outgrowth effects on rat hipocampal and cortical cell and PC12 cells (Example 3), assays to show that EPO mimetic peptides stimulate

neurite outgrowth in cell culture (Example 4), and assays to determine that EPO protects against ischemic injury in rats (Example 5).

Therefore, the instant specification does not commensurate with the claimed subject matter in which the peptides tested for biological activity against EPO receptors *in* vitro is expected to be particularly useful in the treatment of a patient having a condition mediated by neurotoxicity, neurodegeneration or neurological damage which encompass the various diseases and conditions recited on page 16, lines 27 to page 18, lines 30. Examples of the chronic neurodegenerative disorders, or diseases, or conditions intended to be treated by the peptides of the present invention include, but are not limited to, Alzheimer's disease, Pick's disease, diffuse Lewy body disease, progressive spranuclear palsy (Steel-Richardson syndrome), multisystem degeneration (SHY-Drager syndrome), chronic epileptic conditions associated with neurodegeneration, motor neuron diseases including amyotrophic lateral sclerosis, degenerative ataxias, cortical basal degeneration, ALS-Parkinson's-Dementia complex of Guam, subacute sclerosing panencephalitis, Huntington's disease, Parkinson's disease, etc. Examples, of acute neurodegenerative disorders include, but are not limited to, various types of acute neurodegenerative disorders associated with neuronal cell death or compromise including cerebrovascular insufficiency, focal or diffuse brain trauma, diffuse brain damage, and spinal cord injury. With respect to the limitation of a condition mediated by neurotoxicity (claim 1), the claimed invention as recited on page 18, lines 10 to 15 in the instant specification contemplates the treatment and/or prevention of neurological and neuropsychiatric manifestations resulting from chemical,

toxic, infections and radiation injury of the nervous system and as a result of prematurity, as well as the treatment and/or prevention of neurological and neuropsychiatric consequences of encephalopathies including, but not limited to, those of anoxic-ischemia, hepatic, glycemic, uremic, electrolyte and endocrine origin. Thus, there is no working example(s) or evidence or data to show that a similar regimen can be used for treating a patient (including a human) having a condition mediated by neurotoxicity, neurodegeneration or neurological damage such as Alzheimer's disease, Parkinson's disease, Huntington's disease, cerebrovascular insufficiency, anoxic-ischemia, etc., (as recited above) by administering to said patient a therapeutically effective amount of a peptide comprising one or more monmeric peptides of 8 to about 40 amino acids in length that bind to EPO receptor in the manner claimed in claims 1-22.

Thus, in view of the above, and in view of the fact that there is no enablement in the instant specification for the method of treating diseases or conditions of the nervous system in patients by administration of compositions having neurological therapeutic activity of EPO compound claimed, and further in view of the complexity of Applicant's invention and the state of the art of treating and/or preventing of neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, Huntington's disease, cerebrovascular insufficiency, anoxic-ischemia, etc. with the compound claimed; the Examiner is unable to determine the enablement of the invention as claimed without appropriate working example(s) or evidence or data. Such evidence in the art of treating cognitive dysfunctions details the state of the art in this area and establishes

that even some of the diseases such as Alzheimer's disease are very hard to diagnose, let alone to treat and/or prevent. For example, Ezzell (Scientific America, pages 152-153, March 7, 1993) states on page 152, middle column, before last paragraph that doctors can only diagnose Alzheimer's through a process of elimination, ruling out other disorders such as a slight stroke, a brain tumor, or even an adverse drug reaction. A definitive diagnosis must await death and autopsy, when a pathologist can view the telltale "senile plaques" that pock the brains of Alzheimer's victim. Further, Varon et al. (Dev. Neurosci., Vol. 6, pp. 73-100, 1983/1984) discuss the implications of neurotrophic and neurite-promoting factor and their clinical potential in neuronal diseases such as Parkinson, ALS and Alzheimer in which the authors concluded by stating that further clinical progress requires a better understanding of neurobiological bases of nerve regeneration. Furthermore, Cordell et al. (U.S. Patent No. 5,221,607) discuss that the etiology of Alzheimer's disease is unknown and up to date, there are no means available to treat the pathogenesis of Alzheimer's disease and the paucity of understanding concerning the mechanism of amyloid formation in Alzheimer's disease is a major obstacle in the development and design of therapeutic agents that can intervene in this process (See e.g., Col.1, lines 55-67).

Similarly, Nelson et al. (U.S. Patent No. 5,252,463) discuss serious diseases affecting the central nervous system, which referred as neuropathologies such as Alzheimer's disease and Down's syndrome in which the etiology of Alzheimer's disease is unknown (See e.g., column 1). Moreover, WO 99/21966 on page 3, lines15 to 24 states that to date, treatment for CNS disorders has been primarily via the

administration of pharmaceutical compounds. Unfortunately, this type of treatment has been fraught with many complications including the limited ability to transport drugs across the blood-brain barrier and the drug-tolerance, which is acquired by patients to whom these drugs are administered long-term. For instance, Parkinson's patients using levodopa, become tolerant to the effects of levodopa, and therefore, steadily increasing dosages are needed to maintain its effect. In addition, there are a number of side effects associated with levodopa such as increased and uncontrollable movement.

Thus, the prior art clearly show the unpredictable nature and the complexity of the art in regard to treatment and/or prevention of CNS disorders which include Alzheimer's disease, Parkinson's disease, Down's syndrome, Huntington's disease, etc. Therefore, considering the nature of the treatment and/or prevention of CNS disorders and/or diseases by administering a therapeutically effective amount of the peptide claimed and the limited success achieved; one skilled in the art would not accept the instantly claimed invention as obviously valid and correct without demonstration of working example(s) or evidence or data for the following reasons:

In view of the fact that animals and humans are out bred, in view of the lack of disclosure of suitable animal models for a method of treating CNS disorders or conditions or diseases, in view of the recognized problems in the art regarding effective treatment of diseases affecting the nervous systems (neuropathologies) and in view of the fact that it is difficult to regenerate the neurons in the living body; a reasonable doubt exists as to the enablement of the claimed method of treating a patient having a condition mediated by neurotoxicity, neurodegeneration or neurological damage by

administering to said patient (particularly human) a therapeutically effective amount of a peptide comprising one or more monomeric peptides of 8 to about 40 amino acids in length that bind to EPO receptor claimed. Thus, the claims are based on pure speculation that the method would be effective since Applicant has not established any *nexus* between an effective amount of the claimed peptides and its use in the manner claimed.

Further, the first paragraph of 35 U.S.C. 112 requires, *inter alia*, that a patent specification provide sufficient guidance to enable a person skilled in the art to make and use the claimed invention without undue experimentation. *In re Vaeck*, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991). While patent Applicants are not directed to disclose every species that falls within a generic claim, id. At 496, 20 USPQ2d at 1445, it is well settled that "the scope of the claims must bear a reasonable correlation to the scope of the enablement provided by the specification". *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Where practice of the full scope of the claims would require experimentation; factors to be considered in determining whether a disclosure would require undue experimentation ..... include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. *In re Wands*, 858 F. 2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

Therefore, in view of the above, and in view of the fact that there is no enablement in the instant specification for methods of treating diseases of the nervous system by administration of composition having the neurological therapeutic activity of EPO. Thus, applying the *Wands* factors to the facts of this case, one of skill in the art would find that undue amount of experimentation would be required to practice the full scope of the extremely broad claims fro the reasons given above. Hence, in view of the quantity of experimentation necessary, the lack of adequate guidance or working example(s) or data or evidence, and the breadth of the claims, the claims are not commensurate in scope with the enabling disclosure. Accordingly, filing of evidence commensurate with the scope of the claims or amendment of the claims to what is supported by the enabling disclosure is suggested.

CLAIMS REJECTION-35 U.S.C. § 112 2nd PARAGRAPH

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 1-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite in the recitation the acronym "EPO". Use of the full terminology at least in the first occurrence would obviate this rejection.

CLAIMS REJECTION-35 U.S.C. § 103(a)

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Johnson et al., (Biochemistry, Vol. 37, pp. 3699-3710, 1998) taken with Bernaudin et al. (Journal of Cerebral Blood Flow and Metabolism, Vol. 19, pp. 643-651, 1999) and Campana et al., (International Journal of Molecular Medicine, Vol. 1, pp. 235-241, 1998).

The reference of Johnson et al. is directed generally to obtain information about the functional importance of amino acids required for effective erythropoietin (EPO) mimetic action by identifying a minimal mimetic peptide sequence and by generating a series of truncation peptides. The reference has targeted EPO mimetic peptide such as Sequence NO:EMP1 which corresponds to the claimed SEQ ID NO:8 and more than 25 derivatives of this sequence were evaluated for their ability to compete with [^{125}I] EPO for receptor binding and their ability to support the proliferation of two EPO-responsive

cell lines. Further, the reference shows that the mimetic peptides disclosed were subjected to a similar analysis and their competitive binding ability as reported in Tables 1-4. The amino acid sequences disclosed as EMP 1 and EMP 6 to EMP 39 on Tables 1-4 are identical with the claimed SEQ ID NOS:8 and 13-46, respectively. Particularly, elected SEQ ID NOS:8, 19, 20 17 and 21 are EMP 1, EMP 6, EMP 9, EMP 23 and EMP 27, respectively (See e.g., abstract, page 3700, Figures 2-3 and Tables 1-4) as directed to claims 1-15. On page 3701, last paragraph to page 3702, second column, first paragraph and Figures 4 and 5, the reference shows the dimerization of EBP by EPO mimetic peptides, wherein cross linking was used to study the ability of EPO mimetic peptides to mediate the dimerization of the ligand binding domain of the EPO receptor. Thus, the prior art meets the limitations of claims 16-22.

The reference of Johnson et al. differs from claims 1-22 in not teaching a method for treating a patient having a condition mediated by neurotoxicity, neurodegeneration or neurological damage by administering the claimed peptide to a patient, the recited sequence are identical with the prior art sequences. Here, the reference of Bernaudin et al. teaches the role for EPO in focal permanent cerebral ischemia in mice, wherein the EPO/EPO-R system is implicated in the processes of neuroprotection and restructuring (such as angiogenesis and gliosis) after ischemia. As support, a significant reduction in infract volume (47%; $P<0.0002$) was found in mice treated with recombinant EPO 24 hours before induction of cerebral ischemia. Based on this, the reference suggests EPO/EPO-R is an endogenous mechanism that protects the brain against damages consequent to a reduction in blood flow, a mechanism that can be amplified by the intracerebroventricular application of exogenous recombinant EPO (See e.g., abstract and pages 648-650)

The reference of Campana et al. on page 235, col. 2, paragraph 3 identified a 17 amino acid sequence in the predicted A-B loop of EPO which has neurotrophic activity *in vitro* and *in vivo* but lacks EPO activity. The result suggests that there may be more than one functional domain in EPO which confers either neurological or EPO activity. The reference concludes on page 240, last paragraph by stating the results confirmed that EPO enhanced ChAT activity in neural cells. However, the data also demonstrated novel activities of EPO on neutral cells. EPO facilitated neurite sprouting *in vitro*, induced sprouting of motor neurons *in vivo* and elicited signaling through an MAPK cascade. Furthermore, a sequence derived from EPO epopeptide AB, had neurotrophic activity appeared to be EPO receptor mediated, yet it did not enhance proliferation of EPO cells. The identification of a neural specific EPO derived peptide may be useful for targeted neurological studies.

Therefore, in view of the fact that Johnston et al. clearly disclose the known identical sequences with the claimed one, in view of the fact that the secondary reference of Bernaudin et al. teaches the role for EPO in focal permanent cerebral ischemia in mice, wherein the EPO/EPO-R system is implicated in the processes of neuroprotection and restructuring (such as angiogenesis and gliosis) after ischemia, and in view of the fact that the reference of Campana et al. identified a 17 amino acid fragment in the predicted A-B loop of EPO which has neurotrophic activity *in vitro* and *in vivo;* one of ordinary skill in the art would have been motivated to test the various EPO derived peptides to obtain the known and recognized advantages of identifying a neural specific EPO derived peptides for targeting neurological studies as suggested by Campana et al.

Thus, given the combined teachings of the prior art, one of ordinary skill in the art would have been motivated at the time the invention was made to employ the teachings

of the secondary reference of Bernaudin et al. which suggests that EPO/EPO-R system is endogenous mechanism that protects the brain against damages consequent to a reduction in blood flow, a mechanism that can be amplified by the intracerebroventricular application of exogenous recombinant EPO; and, that the secondary reference of Campana et al. identified a 17 amino acid fragments in the predicted A-B loop of EPO which has neurotrophic activity *in vitro* and *in vivo,* and where the primary reference of Johnson et al. discloses identical sequences with the claimed sequences suggests that they should serve as an excellent starting point for the design of compounds with EPO mimetic activity. Based on this, the claimed peptides are known and other peptides are contemplated as acting in the same manner, one of ordinary skill in the art would be prompted to use the peptides from the primary reference of Johnson et al. in combination with other peptides for the intended purposes of treating a patient having a condition mediated by neurotoxicity, neurodegeneration or neurological damage. Thus, the combined teachings of the prior art makes obvious the claimed invention for the reasons discussed above, absent of objective factual evidence or unexpected results to the contrary.

CITATION OF RELEVANT PRIOR ART

6. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Johnson et al. (U.S. Patent No. 5,767,078) teach the dimerization of EPO agonist and antagonist of cell surface receptors and particularly to peptide dimmers, which behave as cell surface receptor agonist in their dimeric form.

Wrighton et al. (U.S. Patent Nos. 5,773,569 and 5,830,851) each patent discloses compositions and methods of administering peptides that bind to EPO receptor, wherein the peptides have 10-40 or more amino acid residues in length and the peptides are used to treat EPO disorders. Further, both patents disclose SEQ ID NO:52, which is identical with the elected and claimed SEQ ID NO:19.

CONCLUSION AND FUTURE CORRESPONDENCE

7. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Abdel A. Mohamed whose telephone number is (703) 308-3966. The examiner can normally be reached on Monday through Friday from 7:30 a.m. to 5:00 p.m. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached on (703) 308-2923. The appropriate fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

CHRISTOPHER S. F. LOW
SUPERVISORY PATENT EXAMINER
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Mohamed/AAM

November 14, 2003